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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,514	04/30/2001	K. Roger Aoki	D2929CON	3428

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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,514	AOKI ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed August 22, 2006. Applicant's submission of copies of case law (In re Crockett, In re Geiger and Exparte Quandranti) is acknowledged. Claims 2-7 and 10-33 have been cancelled. Claims 1, 8 and 9 are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections are withdrawn:

a) rejection of claims 17, 24-25 and 28-31 under 35 U.S.C. 103(a), pages 6-9, paragraph 4 of the previous Office action.

b) rejection of claims 17 and 24-25 under 35 U.S.C. 112, second paragraph, pages 10, paragraph 5 of the previous Office action.

c) rejection of claims 30-31under 35 U.S.C. 112, second paragraph, pages 10, paragraph 6 of the previous Office action.

Rejection Maintained

4. The rejection under 35 U.S.C. 103(a) as unpatentable over Anderson et al in view of Sugiyama et al is maintained for claims 1 and 8-9 for the reasons set forth on pages 3-6, paragraph 4 of the previous Office action.

The rejection was on the grounds that Anderson et al teach a method of treating a patient suffering from spasmodic torticollis comprising administering botulinum toxin A (pages 524-525). Anderson et al teach that three patients developed resistance to the botulinum A treatment and had developed neutralizing antibodies to the botulinum toxin in their serum (page 528). Anderson et al teach that the presence of antibodies does not necessarily preclude further successful botulinum toxin treatment as one patient attending the study who had a high titre of neutralizing antibody responded again when the treatment dose was increased (page 528).

Anderson et al do not teach that treatment of a neuromuscular disorder or condition comprising administering botulinum toxin A in combination with botulinum toxin types B or E.

Sugiyama teaches that the antigenically different botulinum neurotoxins have molecular similarities that would be expected of molecules which have a common unique pharmacological action (page 427). Sugiyama teaches that there is an inverse relationship between specific toxicities and the size of the complexes of a particular toxin type (page 426). Sugiyama teaches that botulinum toxin type B can be proteolytic (comprises both M and L complexes) or non-proteolytic (comprises only M complexes) (page 426). Sugiyama teaches that botulinum toxin E comprises only M complexes (page 426). Sugiyama teaches that purified toxins are more easily detoxified that those in the M complexes (page 427). Sugiyama suggests that synaptosomal receptors to which botulinum toxin types bind may not be the same for all toxin types (page 436).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine botulinum toxin type A as taught by Anderson et al and Botulinum toxin type B or E as taught by Sugiyama et al in the method of treating patients against torticollis because Sugiyama suggests that synaptosomal receptors to which botulinum toxin types bind may not be the same for all toxin types (page 436). Therefore, one of ordinary skill in the art would conclude that a combination of botulinum toxin types would have different affinities on the synaptosomal receptors and thereby be more effective in treating a neuromuscular disorder by blocking the synaptosomal receptors at different areas. The inhibiting or blocking acetylcholine release will leave muscles unable to respond to stimuli that reach them via the motor nerves. It would be expected barring evidence to the contrary that administering a combination of botulinum toxin types A and B or A and E would be effective in treating a neuromuscular disorder such as spasmodic torticollis because Sugiyama teaches that botulinum toxin types B and E can contain only M complexes and these complexes are less likely to become detoxified than purified botulinum toxin.

Additionally, In re Nilssen (7 USPQ 2d 1500) states:

> ...The board attributes to the "hypothetical person" knowledge of all prior art in the filed of the inventor's endeavor and of the prior art solutions for a common problem even if outside that field.

We reject that recommendation as contrary to our precedent, which holds that for the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references.

Moreover, MPEP at section 2144.06 states

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti,25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....

Therefore, "it is *prima facie* obvious to combine two compositions each of which is taught in the art to be used for the very same purpose: idea of combining them flows logically from their having been individually taught in the prior art".

Applicant's Arguments

A) Applicant urges that there is no motivation to combine Anderson et al and Sugiyama et al because Sugiyama et al do not discuss the use of botulinum toxin to treat cervical dystonia or how to overcome antibody formation in patients previously treated with botulinum toxin type A. Applicant urges that even if the two prior art reference were combined, all the combination would teach is that the other botulinum toxin types can be used instead of botulinum toxin type A. Applicant urges that there is

no teaching or suggestion either individually or in a combination to administer simultaneously a botulinum toxin type A and a type B or E.

B) Applicant urges that Sugiyama et al teach that "various botulinum types have different pharmacological characteristics such as toxicities and not a general statement.

C) Applicant urges that the case law (e.g. In re Kerkhoven, In re Crockett, In re Geiger and Exparte Quandranti) addresses only use or combinations of material that are each individually known to provide a particular effect or function.

D) Applicant urges that it appears that it is only hindsight reconstruction of the art that the presently claimed method could be found in a combination of Anderson et al and Sugiyama et al.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 22, 2006 have been fully considered but they are not persuasive.

A) To address Applicant's comment regarding Sugiyama not discussing the use of botulinum toxin to treat cervical dystonia, it should be remembered that this a obviousness-type and it is the combination of reference that teach the claimed invention. Further, it is noted that the pending claims do not recite treating cervical dystonia.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Anderson et al teach botulinum toxin can be used to treat spasmodic torticollis. However, Sugiyama et al provides motivation for the artisan of ordinary skill to combine the teachings of the prior art references because Sugiyama et al teach that different botulinum toxin neurotoxins have molecular similarities that would be expected of molecules which have a common unique pharmacological action (page 427). Sugiyama et al disclose that the similarities among botulinum toxin types include molecular weight, disulfide bonds, a dichain structure and mode of action (paralytic effect) (pages 427-436). The case law, In re Kerkhoven, In re Crocket, In re Geiger and Exparte Quandranti provide support to the Examiner's position because it states that "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....".

To address Applicant's comments regarding the combination of references to arrive at the claimed invention, it should be noted that Sugiyama suggests that synaptosomal receptors to which botulinum toxin types bind may not be the same for all toxin types (page 436). Therefore, one of ordinary skill in the art would conclude that a

combination of botulinum toxin types would have different affinities on the synaptosomal receptors and thereby be more effective in treating a neuromuscular disorder by blocking the synaptosomal receptors at different areas. Thus, a composition comprising a combination of botulinum toxin serotypes would be necessary to provide this function.

B) The Examiner disagrees with Applicant's assertion that "various botulinum types have different pharmacological characteristics is not a general statement". As stated above, the prior art teaches that botulinum toxin serotypes A, B, C1, C2, D, E, F and G have similar molecular weights, structures, and similar modes of action. Therefore, one of ordinary skill in the art would be motivated to combine two or more botulinum toxin serotypes in a composition to arrive at a third composition that can be used for the same purpose.

C) The Examiner agrees with Applicant's assertion that "In re Kerkhoven, In re Crockett, In re Geiger and Exparte Quandranti" cases address only use or combinations of material that are each individually known to provide a particular effect or function.

It should remembered Sugiyama teaches that the similarities among botulinum toxin types include molecular weight, disulfide bonds, a dichain structure and mode of action (paralytic effect) (pages 427-436). Based on the teachings of the prior art and the cited case law, the artisan of ordinary skill would be motivated to combine (serotype A and B or A and E) or any combination of botulinum toxin serotypes since all serotypes

have a similar structure and have same function. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

D) In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

VLF

Vanessa L. Ford
Biotechnology Patent Examiner
November 6, 2006

NITA MINNIFIELD
PRIMARY EXAMINER